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EXAMINER

LAMBERTSON, DAVID A

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/886,171

Applicant(s)

ZARLING ET AL.

Examiner

David A. Lambertson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 20 February 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 3,4,10,11,14,16,17,26 and 29-35 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 3,4,10,11,14,16,17,26 and 29-35 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

Receipt is acknowledged of a reply to the previous Office Action, filed February 20, 2004. Amendments were made to the claims.

Claims 3, 4, 10, 11, 14, 16, 17, 26 and 29-35 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed November 19, 2003, that is not addressed in this action has been withdrawn.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 10, 11, 14, 16, 17, 26, 29, 31-33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 26 recite the phrase "wherein said contacting of step (b) is of said second recombination intermediate with said nuclease." It is unclear if this phrase is meant to indicate that only the second intermediate (i.e., the intermediate obtained immediately prior to the recitation of the phrase in question) is contacted in the manner set forth in step (b) of claim 3, or if the step set forth in step (b) of claim 3 is repeated on the second intermediate (i.e., the step has already been performed once on the first intermediate of claim 3, and is now being performed on the second intermediate obtained in claims 4 and/or 26). This is especially unclear in light of the new interpretation of claim 3 (see for example the interpretation set forth in the rejection of claim

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3 under 35 USC 102(b)), where the contacting step of (b) is not necessarily required to practice the method of claim 3. **This is a new rejection that is not necessitated by amendment.**

Claim 10 recites the phrase "resultant product" in reference to some product in claim 3, 4, 26, 30, 31, 32 or 33. It is unclear what is being considered as the "resultant product," given the plain meaning of the term "resultant" as "something derived from or resulting from something else." In claim 3, there are at least three "resultant products": (a) the first recombination intermediate, (b) the nicked target nucleic acid and (c) the first library of target nucleic acids. In claim 4, at least a fourth and fifth "resultant product" emerges, the second recombination intermediate, as well as a second nicked target nucleic acid; the potential of a third product also exists, if the claim is determined to result in the production of a second library of target nucleic acids (i.e., a library where both the first and second predetermined sequences are "evolved"). It is unclear which of these products is considered to be the "resultant product," and this is further made indefinite by the fact that the term may have different meanings from one claim to the other. For example, if one considers the "resultant product" to mean the first library of target nucleic acids with respect to claim 3, it is unclear if it must necessarily have the same meaning with respect to claims 4, 26, etc. **This is a new rejection that is not necessitated by amendment.**

Claims 31 and 33 recite the phrase "wherein said repeating is on said second library of altered nucleic acids." This phrase is unclear within the context of the claims because of the presence of step (b) where the repeating is performed on the first library of target nucleic acids;

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one cannot ascertain if the repeating step is not to be performed until *after* the second library of altered nucleic acids is obtained (i.e., step b is not performed on the first library of nucleic acids), or if step (b) is to be performed on the first library of nucleic acids and then again on the second library of nucleic acids. **This rejection is necessitated by amendment.**

Claim 32 is rejected under 35 USC 112, second paragraph, as being indefinite for failing to recite a positive process step that refers back to the preamble of the claim. In order for the claimed method to be definite in terms of the metes and bounds of the invention, the claim must recite a method step that provides for the result of the methods as claimed. For example, claim 32 ends by stating, "to form a second library of altered target nucleic acids." However, the method is directed to domain specific evolution, and it is unclear if "domain specific evolution" is obtained by the formation of a second library of altered nucleic acids, or if there are additional method steps required after the formation of the second library of altered nucleic acids that are required to perform "domain specific evolution." It would be remedial for Applicant to indicate at the end of the claim, "wherein domain specific evolution is achieved" or something equivalent. **This rejection is necessitated by amendment.**

Claim 35 recites a step of "introducing the resulting product into cells." It would appear from the claim that the resulting product is a chromosomal sequence, which by definition would already be present in the cell, thus making it unclear what the "introducing the resulting product into cells" actually entails. Alternatively, it is unclear what Applicant intends to mean with the

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term "chromosomal nucleic acid" if it does not mean a "chromosome" as defined in the art. **This rejection is necessitated by amendment.**

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Prior to the rejection of the claims, the Office wishes to clarify the interpretation of the language as set forth in the claims. Specifically, in claim 3(c), the claims state "reassembling and recombining said nicked or target nucleic acid to evolve a first library" (emphasis added). As currently presented, the Office must interpret the claim as also reading on the reassembly and recombination of the target nucleic acid in any form; i.e., there is no requirement that the target nucleic acid form the first recombination intermediate or that it be contacted with a single strand-specific nuclease. As such, the claim as written encompasses any form of recombination on a target nucleic acid. This also regards dependent claims 4, 10, 11, 14, 16, 17, 26 and 29, as one must consider that these claims can correspond to the aspect of claim 3 that reads on any method of recombination. The following rejections are based in part on this interpretation.

Claims 3, 4, 10, 11, 14, 16, 17, 26 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Pati (US 5,948,653, as cited in the previous Office Action). **This is a new rejection that is not necessitated by amendment.**

Pati teaches methods of targeting an exogenous polynucleotide (henceforth targeting polynucleotide) to a target sequence, using a complementary region between the targeting polynucleotide and the target sequence, whereby a homologous recombination event occurs thereby resulting in a modification of the target sequence (see for example column 6, lines 46-52). The targeting event is performed by first selecting the target sequence, and then contacting the target sequence with a recombinase and two single stranded targeting polynucleotides. The single stranded polynucleotides are each substantially complementary to each other and comprise "homology clamp" that is substantially complementary to the target sequence (see for example column 19, lines 19-30). The method is used to generate pools or libraries of variant nucleic acid sequences (see for example column 34, lines 23-26) by using targeting polynucleotides that comprise "mismatches" that are used to introduce the variants into the target sequence (see for example column 34, lines 50-64). In a particular embodiment, these variants are generated in specific protein domains, which is the definition of "domain specific gene evolution" (see for example column 35, lines 13-35). Additionally, Pati discusses that the techniques described therein can be performed "at a particular site or sites, or within a particular region or regions" (see for example column 34, lines 7-11), thereby contemplating using a first and second (or more) set of targeting polynucleotides directed to said site or sites (i.e., more than one). The method described by Pati also contemplates that the target sequence can be present in both an endogenous sequence such as a chromosome (see for example column 7, lines 3-6), or in an

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extrachromosomal sequence (see for example column 29, lines 28-63). Furthermore, the method contemplates making the modifications in either prokaryotic or eukaryotic cells (see for example column 9, lines 21-31 and column 6, lines 54-61). In some embodiments, the targeting polynucleotides are first coated with a recombinase (see for example column 28, lines 25-31). Therefore, Pati anticipates the aforementioned claims.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 30-35 are rejected under 35 U.S.C. 103(a) as being obvious over Pati as applied to claims 3, 4, 10, 14, 11, 16, 17, 26 and 29, in view of delCardayre (US 6,326,204, as indicated in the previous Office Action). **This is a new rejection that is not necessitated by amendment.**



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Pati teaches all of the elements set forth above. However, Pati does not teach repeating the contacting/recombination step.

DelCardayre teaches a method for artificially evolving cells to acquire a new property, where the method comprises successive cycles of recombination events to maximize molecular diversity, using a library of diverse nucleic acid molecules (see for example column 9, lines 23-38 and column 10, lines 35-45). Although delCardayre contemplates that this method can be used for the diversification of genes without the need to focus solely on those genes that have been characterized, delCardayre also teaches that the method can be used in a more focused manner. Specifically, delCardayre recognizes that any individual, specific gene (i.e., a target sequence) can be "evolved" through their described method, which requires reiterative recombination events with a library of nucleic acid sequences (i.e., targeting polynucleotides) (see for example column 16, lines 24-47). Thus, delCardayre provides a general teaching that reiterative cycles of recombination can be utilized to evolve a gene.

The ordinary skilled artisan would recognize that the teachings of both delCardayre and Pati involve the forced evolution of genes using a process of recombination between targeting polynucleotides and a target sequence, therefore it would be obvious to combine the teachings of delCardayre and Pati because they both use the same general techniques in order to accomplish the same goal. The ordinary skilled artisan would have been motivated to combine the teachings in order to achieve the most advantageous level of evolution/molecular diversity of the target sequence, which is suggested by the multiple rounds of recombination practiced in the teachings of delCardayre. Absent evidence to the contrary, and in light of the interrelated nature of the

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teachings of delCardayre and Pati, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the claimed invention.

One of the applied references has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

### ***Response to Arguments***

Applicant's arguments with respect to the rejection under 35 USC 103(a) are moot in view of the new ground(s) of rejection, which are predicated on the interpretation of the claimed

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invention as set forth in the rejections under 35 USC 102(e). In view of the Office's more accurate interpretation of the claims, the rejections must now be applied to the claims that were previously un-rejected.

***Allowable Subject Matter***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JAMES KETTER  
PRIMARY EXAMINER